

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 18 August 2000 (18.08.00)	
<b>International application No.</b> PCT/US99/30491	<b>Applicant's or agent's file reference</b> 5940-01-EDS
<b>International filing date</b> (day/month/year) 21 December 1999 (21.12.99)	<b>Priority date</b> (day/month/year) 13 January 1999 (13.01.99)
<b>Applicant</b> TECLE, Haile et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 20 July 2000 (20.07.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Henrik Nyberg  Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

NOTED

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PCT

From the INTERNATIONAL SEARCHING AUTHORITY AUG 07 2000

To:  
**WARNER-LAMBERT COMPANY**  
 Attn. RYAN, M. Andrea  
 201 Tabor Road  
 Morris Plains, New Jersey 07950  
 UNITED STATES OF AMERICA

**R. ARMSTRONG** NOTIFICATION OF TRANSMITTAL OF  
 THE INTERNATIONAL SEARCH REPORT  
 OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing  
 (day/month/year) **31/07/2000**

Applicant's or agent's file reference  
**5940-01-EDS**

**FOR FURTHER ACTION** See paragraphs 1 and 4 below

International application No.  
**PCT/US 99/ 30491**

International filing date  
 (day/month/year) **21/12/1999**

Applicant  
**WARNER-LAMBERT COMPANY et al.**

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name

Form

*Provisional  
 no need to  
 send new*

International Searching Authority  
 318 Patentlaan 2  
 651 epo nl,

Authorized officer  
**Chantal Meyer**

Express Mail No. EJ881683560US  
 PD-5940-01-SMH

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>5940-01-EDS</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/ 30491</b>	International filing date (day/month/year) <b>21/12/1999</b>	(Earliest) Priority Date (day/month/year) <b>13/01/1999</b>
Applicant <b>WARNER-LAMBERT COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**ANTHRANILIC ACID DERIVATIVES**

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority:

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

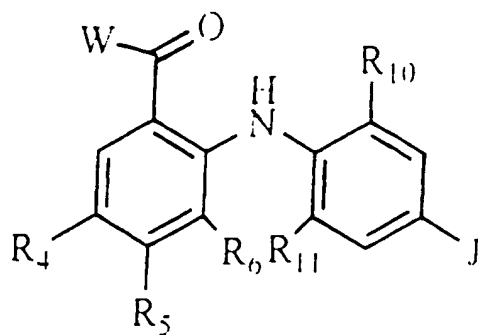
☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The invention features a compound having the formula (I) below:



(I)

The invention also relates to a pharmaceutical composition including

(a) a compound of formula (I) and (b) a pharmaceutically-acceptable carrier

The invention further relates to a method for treating proliferative diseases, such as cancer, restenosis, psoriasis, autoimmune disease, and atherosclerosis. Other aspects of the invention include methods for treating MEK-related (including ras-related) cancers, whether solid or hematopoietic.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30491

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C323/38 C07C317/36 C07D233/61 C07D285/10 C07C229/58  
C07C259/06 A61K31/195 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, BEILSTEIN Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>a</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 316 630 A (WARNER-LAMBERT CO) 24 May 1989 (1989-05-24)  page 8, lines 3-55; examples 13, 18; claims 1-4, 9, 14, 15, 17 --- -/--	1, 2, 4, 8, 17, 29-32, 35-40

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.<sup>a</sup> Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

14 July 2000

Date of mailing of the international search report

31/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Van Amsterdam, L

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30491

C.(Continuation) DOCUMENT CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  STN, CAPLUS accession no. 1969:11330,  XP002142609  abstract; RN 20885-73-8, 20885-75-0,  20885-79-4  -&amp; CHEMICAL ABSTRACTS, vol. 70, no. 3,  20 January 1969 (1969-01-20)  Columbus, Ohio, US;  abstract no. 11330,  XP002142605  abstract  &amp; JP 42 024578 B (TAKEDA CHEMICAL  INDUSTRIES LTD)  25 November 1967 (1967-11-25)</p>	1,2,4,6, 8,17,29
X	<p>DATABASE CHEMABS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  STN, CAPLUS accession no. 1972:121461,  XP002142610  abstract; RN 13501-67-2, 16524-23-5,  27210-58-8, 35958-19-1  &amp; N.A. MOKHORT: FARMAKOL. TOKSIKOL.  (KIEV),  no. 6, 1971, pages 108-111,</p>	1-3,6,8, 9,15,16, 29
X	<p>US 4 510 139 A (D.M. BAILEY)  9 April 1985 (1985-04-09)</p> <p>column 3, lines 24-21; examples 1, 3, 5,  7-14, 17, 19, 21, 24, 25, 27</p>	1-3,6,8, 15,16, 18,29,30
X	<p>DATABASE CHEMABS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  STN, CAPLUS accession no. 1968:418858,  XP002142611  abstract; RN 19093-89-1  &amp; JP 42 019583 B (TAKEDA CHEMICAL  INDUSTRIES LTD)  25 November 1967 (1967-11-25)</p>	1-3,8, 11,15, 16,29
X	<p>DATABASE CHEMABS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  STN, CAPLUS accession no. 1974:70488.  XP002142612  abstract; RN 4974-76-9, 51679-41-5.  51679-42-6, 51679-46-0, 51679-50-6.  51679-53-9  &amp; E.S. ENDELMAN ET AL: KHIM.-FARM. ZH. ,  vol. 7, no. 12, 1973, pages 15-19,</p>	1,3,8, 15,16,29

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30491

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 242 559 A (HOECHST AG) 28 October 1987 (1987-10-28) page 3, compounds 1, 5, 9; claims 1, 2, 4-6 ---	1-3,8,9, 15,16,29
X	US 2 502 451 A (A.A. GOLDBERG ET AL) 4 April 1950 (1950-04-04) column 2, lines 1-3, 13-17; column 3, lines 42-44; examples 2-4 ---	1-3,8, 15,16,29
X	US 2 553 914 A (A.A. GOLDBERG) 22 May 1951 (1951-05-22) column 3, lines 12-17; examples 1-8, 10-13 ---	1,3,8, 15,16,29
P,X	WO 99 21840 A (WARNER LAMBERT CO) 6 May 1999 (1999-05-06) examples M, O, V ---	1-3,8, 15,16,22
X	DATABASE CROSSFIRE 'Online! BEILSTEIN INSTITUT FUER LITERATUR DER ORGANISCHEN CHEMIE; XP002142613 abstract; BRN 3350527 ---	1-3,8, 12,15,16
X	US 2 082 171 A (F. MIETZSCH ET AL) 1 June 1937 (1937-06-01) page 2, column 2, lines 19-22; page 3, column 1, lines 7-10, 66-69 ---	1-3,8,9, 15,16
X	US 3 781 358 A (E.L. ANDERSON ET AL) 25 December 1973 (1973-12-25) column 3, lines 69-70; column 4, lines 30-31; column 6, lines 24-25, 51-52; column 7, lines 19-20, 44-45 ---	1-3,8,9, 15,16
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAOLD accession no. 8753f, XP002142614 RN 798-84-5 -& CHEMICAL ABSTRACTS, vol. 59, no. 8, 14 October 1963 (1963-10-14) Columbus, Ohio, US; abstract no. 8753f, XP002142606 abstract & F. HUNZIKER ET AL: ARZNEIMITTEL-FORSCH., vol. 13, 1963, pages 324-328, ---	1,3,8,9, 15,16
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30491

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1969:403368, XP002142615 abstract; RN 22777-13-5, 22777-15-7 & M. TAKEDA ET AL: YAKUGAKU ZASSHI, vol. 89, no. 2, 1969, pages 158-163, ----	1-3,8, 15,16
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAOLD accession no. 35:7965h, XP002142616 RN 2925-86-2, 2925-87-3 abstract -& CHEMICAL ABSTRACTS, vol. 35, no. 22, 20 November 1941 (1941-11-20) Columbus, Ohio, US; abstract no. 7965h, XP002142607 abstract & V.O. YU ET AL: J. GEN. CHEM. USSR, vol. 11, 1941, pages 243-253, ----	1-3,6,8, 15,16, 19,22
X	CHEMICAL ABSTRACTS, vol. 38, no. 1, 10 January 1944 (1944-01-10) Columbus, Ohio, US; abstract no. 105, XP002142608 abstract no 105, 7-9 & A.H. COOK ET AL: J. CHEM. SOC., 1943, pages 417-419, ----	1,3,8, 15,16
X	DE 21 55 106 A (CIBA-GEIGY AG) 10 May 1972 (1972-05-10) page 4, line 10; examples 1-2; claims 1-3 ----	1,3,8, 15,16
A	WO 98 37881 A (WARNER LAMBERT CO) 3 September 1998 (1998-09-03) claims; examples -----	1,29,45

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/30491

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 30-50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/30491

Patent document cited in search report		Publication date	Patent member(s)	Publication date
EP 316630	A	24-05-1989	US 5155110 A AU 2909289 A WO 8903818 A ZA 8807696 A	13-10-1992 23-05-1989 05-05-1989 27-06-1990
US 4510139	A	09-04-1985	US 4549016 A	22-10-1985
JP 42019583	B		NONE	
EP 242559	A	28-10-1987	DE 3608726 A DK 131187 A JP 62221659 A PT 84457 A,B US 4921875 A	17-09-1987 16-09-1987 29-09-1987 01-04-1987 01-05-1990
US 2502451	A	04-04-1950	FR 930361 A GB 608492 A NL 62219 C	28-01-1948
US 2553914	A	22-05-1951	NONE	
WO 9921840	A	06-05-1999	AU 9503998 A ZA 9809783 A	17-05-1999 28-04-1999
US 2082171	A	01-06-1937	NONE	
US 3781358	A	25-12-1973	US 3692834 A US 3919312 A GB 1202138 A US 3625945 A	19-09-1972 11-11-1975 12-08-1970 07-12-1971
DE 2155106	A	10-05-1972	BE 774961 A CA 967151 A CH 541608 A ES 396691 A FR 2113616 A GB 1371378 A IT 946042 B NL 7115291 A	05-05-1972 06-05-1975 31-10-1973 01-01-1975 23-06-1972 23-10-1974 21-05-1973 09-05-1972
WO 9837881	A	03-09-1998	AU 5610398 A ZA 9801578 A	18-09-1998 02-09-1998

## PATENT COOPERATION TREATY

CC: Rose Armstrong  
Charles Ashbrook

5940 SMH

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

09/889100

PCT

To:

MANSMANN, Ivo et al  
Warner-Lambert Company  
Legal Division  
c/o Gödecke AG, Patents  
Mooswaldallee 1  
D-79090 Freiburg  
ALLEMAGNE

Patentwesen

Eing.: 30. März 2001

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing

(day/month/year)

29.03.2001

Applicant's or agent's file reference  
5940-01-EDS

## IMPORTANT NOTIFICATION

International application No.  
PCT/US99/30491

International filing date (day/month/year)  
21/12/1999

Priority date (day/month/year)  
13/01/1999

Applicant

WARNER-LAMBERT COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

## 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
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## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>5940-01-EDS</b>		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/US99/30491</b>	International filing date (day/month/year) <b>21/12/1999</b>	Priority date (day/month/year) <b>13/01/1999</b>	
International Patent Classification (IPC) or national classification and IPC <b>C07C323/00</b>			
Applicant <b>WARNER-LAMBERT COMPANY et al.</b>			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 10 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input checked="" type="checkbox"/> Certain defects in the international application</p> <p>VIII <input checked="" type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand  <b>20/07/2000</b>		Date of completion of this report  <b>29.03.2001</b>	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer  <b>Bedel, C</b>  Telephone No. +49 89 2399 2506 	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/30491

**1. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

**Description, pages:**

1-42 as originally filed

**Claims, No.:**

1-50 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/30491

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 30-50.

because:

- ☒ the said international application, or the said claims Nos. 30-50 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,7,10,13-14,20-21,30-50
	No:	Claims	1-4,6,8,9,11,12,15-19,22,29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-29



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/30491

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No: Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/30491

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 30-50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 30-50 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: EP-A-0 316 630 (WARNER-LAMBERT CO) 24 May 1989 (1989-05-24)
- D2: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1969:11330, XP002142609 -& CHEMICAL ABSTRACTS, vol. 70, no. 3, 20 January 1969 (1969-01-20) Columbus, Ohio, US; abstract no. 11330, XP002142605 & JP 42 024578 B (TAKEDA CHEMICAL INDUSTRIES LTD) 25 November 1967 (1967-11-25)
- D3: US-A-4 510 139 (D.M. BAILEY) 9 April 1985 (1985-04-09)
- D4: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1968:418858, XP002142611 & JP 42 019583 B (TAKEDA CHEMICAL INDUSTRIES LTD) 25 November 1967 (1967-11-25)
- D5: EP-A-0 242 559 (HOECHST AG) 28 October 1987 (1987-10-28)
- D6: US-A-2 502 451 (A.A. GOLDBERG ET AL) 4 April 1950 (1950-04-04)

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/30491

- D7: US-A-2 553 914 (A.A. GOLDBERG) 22 May 1951 (1951-05-22)
- D8: WO 99 21840 A (WARNER LAMBERT CO) 6 May 1999 (1999-05-06)
- D9: US-A-2 082 171 (F. MIETZSCH ET AL) 1 June 1937 (1937-06-01)
- D10: US-A-3 781 358 (E.L. ANDERSON ET AL) 25 December 1973 (1973-12-25)
- D11: DE 21 55 106 A (CIBA-GEIGY AG) 10 May 1972 (1972-05-10)
- D12: WO 98 37881 A (WARNER LAMBERT CO) 3 September 1998 (1998-09-03)
- D13: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1972:121461, XP002142610 & N.A. MOKHORT: FARMAKOL. TOKSIKOL. (KIEV), no. 6, 1971, pages 108-111,
- D14: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1974:70488, XP002142612 & E.S. ENDELMAN ET AL: KHIM.-FARM. ZH. , vol. 7, no. 12, 1973, pages 15-19,
- D15: DATABASE CROSSFIRE [Online] BEILSTEIN INSTITUT FUER LITERATUR DER ORGANISCHEN CHEMIE; XP002142613
- D16: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAOLD accession no. 8753f, XP002142614 -& CHEMICAL ABSTRACTS, vol. 59, no. 8, 14 October 1963 (1963-10-14) Columbus, Ohio, US; abstract no. 8753f, XP002142606 & F. HUNZIKER ET AL: ARZNEIMITTEL-FORSCH., vol. 13, 1963, pages 324-328,
- D17: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1969:403368, XP002142615 & M. TAKEDA ET AL: YAKUGAKU ZASSHI, vol. 89, no. 2, 1969, pages 158-163,
- D18: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAOLD accession no. 35:7965h, XP002142616 -& CHEMICAL ABSTRACTS, vol. 35, no. 22, 20 November 1941 (1941-11-20) Columbus, Ohio, US; abstract no. 7965h, XP002142607 & V.O. YU ET AL: J. GEN. CHEM. USSR, vol. 11, 1941, pages 243-253,
- D19: CHEMICAL ABSTRACTS, vol. 38, no. 1, 10 January 1944 (1944-01-

10) Columbus, Ohio, US; abstract no. 105, XP002142608 & A.H.  
COOK ET AL: J. CHEM. SOC., 1943, pages 417-419,

**1. Novelty**

The subject-matter of claims 1-4, 6, 8, 9, 11, 12, 15-19, 22, 29 does not comply with the requirements of Article 33(2) PCT for the following reasons :

- ★ Document D1 in examples 13, 18, in claim 9 (10th and 14th compound) and claims 1-4 and 14 (overlapping domains) discloses compounds or group of compounds which anticipate the subject-matter of claims 1,2,4,8,17 and 29.
- ★ Document D2 discloses 2 hydroxamic acid derivatives (R= p-ethoxyphenyl and 4-methylphenyl) which fall within the scope of claims 1,2,4,6,8,17 and 29.
- ★ Document D3 describes 3 benzoic acid derivatives (groups OCH<sub>3</sub>, CH<sub>3</sub> and SCH<sub>3</sub> in para position, corresponding to J in the present application) which anticipate the subject-matter of claims 1-3,6,8,9,15,16 and 29.
- ★ Document D4 in examples 1,3,5,7-14,17,19,21,24,25,27 and column 3, lines 24-31 (pharmaceutical) describes a series of compounds which anticipate the subject-matter of claims 1-3,6,8,15,16,18-29.
- ★ Document D5 discloses a benzoic acid derivative comprising a 4-methylsulfonyl group (equivalent to J group in application), thus anticipating the subject-matter of claims 1-3,8,11,15,16,29.
- ★ Document D6 discloses a benzoic acid derivative with a 4-trifluoromethyl sulfonyl group, which destroys the novelty of claims 1,3,8,15,16 and 29.
- ★ Document D7 at page 3, discloses compounds 1,5 and 9 and in claims 1,2, 4-6 which overlap with the subject-matter of claims 1-3,8,9,15,16,29.
- ★ Document D8 at column 2, lines 1-3 and 13-17 (see also examples 2-4) discloses compounds which anticipate the subject-matter of claims 1-3,8,15,16 and 29 (see col.3, l.42-44).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/30491

- ★ Document D9 in examples 1-8 and 12-14 discloses compounds which anticipate the subject-matter of claims 1,3,8,15,16, these compounds being used as pharmaceuticals (col.3, l.12-14), the subject-matter of claim 29 is anticipated as well.
- ★ Document D11 discloses a compound which anticipates the subject-matter of claims 1-3,8,12,15 and 16.
- ★ Document D12 at page 2, column 2, lines 19-20 and page 3, column 1, lines 7,8 and lines 65,66 discloses compounds which destroy the novelty of claims 1-3,8,9,15 and 16.
- ★ Document D13 in examples 2 ( line 70), 3 (lines 30, 31), 9 (lines 24, 25), 10 (lines 51,52), 12 (lines 19, 29) and 13 (lines 44, 45) discloses compounds which anticipate the subject-matter of claims 1-3,8,9,15 and 16.
- ★ Document D14 discloses a series of compounds of formula (I) (see 8753 f-g and 8754 a) which destroy the novelty of claims 1,3,8,9,15,16.
- ★ Document D15 discloses a compound of Formula (I) which anticipates the subject-matter of claims 1-3,8,15,16.
- ★ Document D16 discloses a compound which falls within the scope of claims 1-3,6,8,15,16,19 and 22.
- ★ Document D17 discloses a compound of formula (I) (see 105-7) which anticipates the subject-matter of claims 1,3,8,15,16.
- ★ Document D18 at page 4, line 10, in example 1, line 8,9 and example 2 (see formula) discloses compounds (and domain of compounds see claims 1,2) which anticipate the subject-matter of claims 1,3,8,15,16.

**2. Inventive step**

Furthermore, the subject-matter of claims 1-50 cannot be considered as inventive

for the following reasons :

D19 can be considered as the closest prior art as it discloses compounds which shows MEK enzyme inhibition, these compounds differing by the fact that the para group of the phenylamine moiety is Br or I in D19 while it is a "J" group as defined in claim 1 of the present application.

The technical problem can be considered as providing alternative compounds which show some inhibition properties on MEK enzyme which is known to be involved in **immunomodulation, inflammation and proliferative diseases** (see application page 1, line 9).

This technical problem has been solved by the compounds of formula (I) wherein the Br or I group have been replaced by a "J" group.

However, compounds comprising such a "J" group have been already disclosed and exhibit some antiinflammation (see D2-D6) or antiproliferative properties (see D4, column 13, line 4). Although these documents do not explicitly refer to a specific inhibition of MEK enzyme by these compounds (probably because the mechanism of action of these drugs was not fully known at that time), their pharmacologic properties represent a sufficient hint for a skilled person wishing to develop alternative compounds to the one of D19 in the hope of getting MEK enzyme inhibitors and consequently antiproliferative or antiinflammatory compounds.

**Re Item VII**

**Certain defects in the international application**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D19 is not mentioned in the description, nor is this document identified therein.

**Re Item VIII**

**Certain observations on the international application**

1. There is a discrepancy between independent claim 1 and claims 23,24 and 28

wherein several compounds of formula I (see claim 1) with  $R_5 = \text{NO}_2$  are claimed, although  $\text{NO}_2$  is not mentioned in the definition for  $R_5$  as given in claim 1. This discrepancy renders the scope of claim 1 unclear, contrary to Article 6 PCT.

2. Claim 4 is not supported by the description since the corresponding passage in the description stipulates that  $W = \text{NHOR}_1$ , which is of a larger scope than the subject-matter of claim 4 ( $\text{NHOH}$ ), contrary to Article 6 PCT.
3. There is another discrepancy between the description page 8 line 9 ("C3-8 alkynyl") and claim 13 ("C2-8 alkynyl"), which leads to a lack of clarity for the subject-matter of the said claim. Another discrepancy of the same kind has been detected : "C3-4 alkynyl" in the description (p.8, l.16) compared to claim 18 "C2-4 alkynyl".
4. Furthermore, claim 21 defines " $R_4$  and  $R_5 = \text{F}$  and  $R = \text{Br}$ " while the corresponding passage in the description reads " $R_5$  and  $R_6$  is  $\text{F}$  and  $R_6$  is  $\text{Br}$ " (see page 8 line 20). A similar mistake appears again on page 8, line 20-21 "each  $R_5$  and  $R_6$  is  $\text{F}$  and  $R_6$  is  $\text{H}$ ".
5. The embodiment of claim 22 wherein  $R_5$  is  $\text{F}$  does not seem to be supported by the description (Article 6 PCT).
6. This holds true for the lists of compounds of claims 24, 25 and 27 (lack of support, Article 6 PCT).
7. The vague and imprecise statement in the description on page 22 (chapter F) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

09/889106

PATENT COOPERATION TREATY

PCT

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5940-01-EDS	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/30491	International filing date (day/month/year) 21/12/1999	Priority date (day/month/year) 13/01/1999
International Patent Classification (IPC) or national classification and IPC C07C323/00		
Applicant WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 10 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  20/07/2000	Date of completion of this report  29.03.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Bedel, C  Telephone No. +49 89 2399 2506  



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/30491

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-42 as originally filed

**Claims, No.:**

1-50 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/30491

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 30-50.

because:

☒ the said international application, or the said claims Nos. 30-50 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5,7,10,13-14,20-21,30-50
	No:	Claims	1-4,6,8,9,11,12,15-19,22,29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-29

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/30491

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No: Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/US99/30491

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 30-50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 30-50 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents:

- D1: EP-A-0 316 630 (WARNER-LAMBERT CO) 24 May 1989 (1989-05-24)
- D2: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1969:11330, XP002142609 - & CHEMICAL ABSTRACTS, vol. 70, no. 3, 20 January 1969 (1969-01-20) Columbus, Ohio, US; abstract no. 11330, XP002142605 & JP 42 024578 B (TAKEDA CHEMICAL INDUSTRIES LTD) 25 November 1967 (1967-11-25)
- D3: US-A-4 510 139 (D.M. BAILEY) 9 April 1985 (1985-04-09)
- D4: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1968:418858, XP002142611 & JP 42 019583 B (TAKEDA CHEMICAL INDUSTRIES LTD) 25 November 1967 (1967-11-25)
- D5: EP-A-0 242 559 (HOECHST AG) 28 October 1987 (1987-10-28)
- D6: US-A-2 502 451 (A.A. GOLDBERG ET AL) 4 April 1950 (1950-04-04)

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/30491

- D7: US-A-2 553 914 (A.A. GOLDBERG) 22 May 1951 (1951-05-22)
- D8: WO 99 21840 A (WARNER LAMBERT CO) 6 May 1999 (1999-05-06)
- D9: US-A-2 082 171 (F. MIETZSCH ET AL) 1 June 1937 (1937-06-01)
- D10: US-A-3 781 358 (E.L. ANDERSON ET AL) 25 December 1973 (1973-12-25)
- D11: DE 21 55 106 A (CIBA-GEIGY AG) 10 May 1972 (1972-05-10)
- D12: WO 98 37881 A (WARNER LAMBERT CO) 3 September 1998 (1998-09-03)
- D13: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1972:121461, XP002142610 & N.A. MOKHORT: FARMAKOL. TOKSIKOL. (KIEV), no. 6, 1971, pages 108-111,
- D14: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1974:70488, XP002142612 & E.S. ENDELMAN ET AL: KHIM.-FARM. ZH. , vol. 7, no. 12, 1973, pages 15-19,
- D15: DATABASE CROSSFIRE [Online] BEILSTEIN INSTITUT FUER LITERATUR DER ORGANISCHEN CHEMIE; XP002142613
- D16: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAOLD accession no. 8753f, XP002142614 -& CHEMICAL ABSTRACTS, vol. 59, no. 8, 14 October 1963 (1963-10-14) Columbus, Ohio, US; abstract no. 8753f, XP002142606 & F. HUNZIKER ET AL: ARZNEIMITTEL-FORSCH., vol. 13, 1963, pages 324-328,
- D17: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAPLUS accession no. 1969:403368, XP002142615 & M. TAKEDA ET AL: YAKUGAKU ZASSHI, vol. 89, no. 2, 1969, pages 158-163,
- D18: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STN, CAOLD accession no. 35:7965h, XP002142616 -& CHEMICAL ABSTRACTS, vol. 35, no. 22, 20 November 1941 (1941-11-20) Columbus, Ohio, US; abstract no. 7965h, XP002142607 & V.O. YU ET AL: J. GEN. CHEM. USSR, vol. 11, 1941, pages 243-253,
- D19: CHEMICAL ABSTRACTS, vol. 38, no. 1, 10 January 1944 (1944-01-

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/30491

10) Columbus, Ohio, US; abstract no. 105, XP002142608 & A.H.  
COOK ET AL: J. CHEM. SOC., 1943, pages 417-419,

**1. Novelty**

The subject-matter of claims 1-4, 6, 8, 9, 11, 12, 15-19, 22, 29 does not comply with the requirements of Article 33(2) PCT for the following reasons :

- ★ Document D1 in examples 13, 18, in claim 9 (10th and 14th compound) and claims 1-4 and 14 (overlapping domains) discloses compounds or group of compounds which anticipate the subject-matter of claims 1,2,4,8,17 and 29.
- ★ Document D2 discloses 2 hydroxamic acid derivatives (R= p-ethoxyphenyl and 4-methylphenyl) which fall within the scope of claims 1,2,4,6,8,17 and 29.
- ★ Document D3 describes 3 benzoic acid derivatives (groups OCH<sub>3</sub>, CH<sub>3</sub> and SCH<sub>3</sub> in para position, corresponding to J in the present application) which anticipate the subject-matter of claims 1-3,6,8,9,15,16 and 29.
- ★ Document D4 in examples 1,3,5,7-14,17,19,21,24,25,27 and column 3, lines 24-31 (pharmaceutical) describes a series of compounds which anticipate the subject-matter of claims 1-3,6,8,15,16,18-29.
- ★ Document D5 discloses a benzoic acid derivative comprising a 4-methylsulfonyl group (equivalent to J group in application), thus anticipating the subject-matter of claims 1-3,8,11,15,16,29.
- ★ Document D6 discloses a benzoic acid derivative with a 4-trifluoromethyl sulfonyl group, which destroys the novelty of claims 1,3,8,15,16 and 29.
- ★ Document D7 at page 3, discloses compounds 1,5 and 9 and in claims 1,2, 4-6 which overlap with the subject-matter of claims 1-3,8,9,15,16,29.
- ★ Document D8 at column 2, lines 1-3 and 13-17 (see also examples 2-4) discloses compounds which anticipate the subject-matter of claims 1-3,8,15,16 and 29 (see col.3, l.42-44).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/30491

- ★ Document D9 in examples 1-8 and 12-14 discloses compounds which anticipate the subject-matter of claims 1,3,8,15,16, these compounds being used as pharmaceuticals (col.3, l.12-14), the subject-matter of claim 29 is anticipated as well.
- ★ Document D11 discloses a compound which anticipates the subject-matter of claims 1-3,8,12,15 and 16.
- ★ Document D12 at page 2, column 2, lines 19-20 and page 3, column 1, lines 7,8 and lines 65,66 discloses compounds which destroy the novelty of claims 1-3,8,9,15 and 16.
- ★ Document D13 in examples 2 ( line 70), 3 (lines 30, 31), 9 (lines 24, 25), 10 (lines 51,52), 12 (lines 19, 29) and 13 (lines 44, 45) discloses compounds which anticipate the subject-matter of claims 1-3,8,9,15 and 16.
- ★ Document D14 discloses a series of compounds of formula (I) (see 8753 f-g and 8754 a) which destroy the novelty of claims 1,3,8,9,15,16.
- ★ Document D15 discloses a compound of Formula (I) which anticipates the subject-matter of claims 1-3,8,15,16.
- ★ Document D16 discloses a compound which falls within the scope of claims 1-3,6,8,15,16,19 and 22.
- ★ Document D17 discloses a compound of formula (I) (see 105-7) which anticipates the subject-matter of claims 1,3,8,15,16.
- ★ Document D18 at page 4, line 10, in example 1, line 8,9 and example 2 (see formula) discloses compounds (and domain of compounds see claims 1,2) which anticipate the subject-matter of claims 1,3,8,15,16.

**2. Inventive step**

Furthermore, the subject-matter of claims 1-50 cannot be considered as inventive

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/30491

for the following reasons :

D19 can be considered as the closest prior art as it discloses compounds which shows MEK enzyme inhibition, these compounds differing by the fact that the para group of the phenylamine moiety is Br or I in D19 while it is a "J" group as defined in claim 1 of the present application.

The technical problem can be considered as providing alternative compounds which show some inhibition properties on MEK enzyme which is known to be involved in **immunomodulation, inflammation and proliferative diseases** (see application page 1, line 9).

This technical problem has been solved by the compounds of formula (I) wherein the Br or I group have been replaced by a "J" group.

However, compounds comprising such a "J" group have been already disclosed and exhibit some antiinflammation (see D2-D6) or antiproliferative properties (see D4, column 13, line 4). Although these documents do not explicitly refer to a specific inhibition of MEK enzyme by these compounds (probably because the mechanism of action of these drugs was not fully known at that time), their pharmacologic properties represent a sufficient hint for a skilled person wishing to develop alternative compounds to the one of D19 in the hope of getting MEK enzyme inhibitors and consequently antiproliferative or antiinflammatory compounds.

**Re Item VII**

**Certain defects in the international application**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D19 is not mentioned in the description, nor is this document identified therein.

**Re Item VIII**

**Certain observations on the international application**

1. There is a discrepancy between independent claim 1 and claims 23, 24 and 28



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/30491

wherein several compounds of formula I (see claim 1) with  $R_5 = \text{NO}_2$  are claimed, although  $\text{NO}_2$  is not mentioned in the definition for  $R_5$  as given in claim 1. This discrepancy renders the scope of claim 1 unclear, contrary to Article 6 PCT.

2. Claim 4 is not supported by the description since the corresponding passage in the description stipulates that  $W = \text{NHOR}_1$ , which is of a larger scope than the subject-matter of claim 4 ( $\text{NHOH}$ ), contrary to Article 6 PCT.
3. There is another discrepancy between the description page 8 line 9 ("C3-8 alkynyl") and claim 13 ("C2-8 alkynyl"), which leads to a lack of clarity for the subject-matter of the said claim. Another discrepancy of the same kind has been detected : "C3-4 alkynyl" in the description (p.8, l.16) compared to claim 18 "C2-4 alkynyl".
4. Furthermore, claim 21 defines " $R_4$  and  $R_5 = \text{F}$  and  $R = \text{Br}$ " while the corresponding passage in the description reads " $R_5$  and  $R_6$  is  $\text{F}$  and  $R_6$  is  $\text{Br}$ " (see page 8 line 20). A similar mistake appears again on page 8, line 20-21 "each  $R_5$  and  $R_6$  is  $\text{F}$  and  $R_6$  is  $\text{H}$ ".
5. The embodiment of claim 22 wherein  $R_5$  is  $\text{F}$  does not seem to be supported by the description (Article 6 PCT).
6. This holds true for the lists of compounds of claims 24, 25 and 27 (lack of support, Article 6 PCT).
7. The vague and imprecise statement in the description on page 22 (chapter F) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).